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MDR-TB screening in a setting with molecular diagnostic techniques: who got tested, who didn't and why?

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Setting: The Revised National Tuberculosis Control Programme, Puducherry, India, which has facilities for molecular diagnostic technique.

Objective: To determine pre-diagnostic and pre-treatment attrition among presumptive multidrug-resistant tuberculosis (MDR-TB) patients and reasons for attrition.

Methods: In this mixed-methods study, the quantitative component consisted of retrospective cohort analysis through record review of all presumptive MDR-TB patients recorded between October 2012 and September 2013. The qualitative component included in-depth interviews with key informants involved in programmatic management of drug-resistant tuberculosis services.

Results: Of 341 eligible presumptive MDR-TB patients, pre-diagnostic and pre-treatment attrition was respectively 45.5% (155/341) and 29% (2/7). Patients with extra-pulmonary TB (RR = 2.3), those with human immunodeficiency and TB co-infection (RR = 1.7), those registered during October–December 2012 (RR = 1.3) and those identified from primary/secondary health centres (RR = 1.8) were less likely to be tested. Themes that emerged during the analysis of the qualitative data were 'lack of a systematic mechanism to track referrals for culture and drug susceptibility testing', 'absence of courier service to transport sputum', 'lack of knowledge and ownership among staff of general health system', 'shortage of diagnostic kits' and 'patient non-adherence'.

Conclusion: Despite the introduction of molecular diagnostic techniques, operational issues in MDR-TB screening remain a concern and require urgent attention.

Tuberculosis (TB) is a major global public health problem, and the increase in multidrug-resistant tuberculosis (MDR-TB) is a growing concern. India accounts for nearly a quarter of the global TB burden and has an estimated 64 000 of the 300 000 MDR-TB cases identified annually worldwide among notified pulmonary TB cases.[1] India's Revised National Tuberculosis Control Programme (RNTCP) has adopted the global Stop TB Strategy-recommended programmatic management of drug-resistant TB (PMDT) for the effective delivery of services for drug-resistant TB.[2] Prompt identification of presumptive MDR-TB patients eligible for drug susceptibility testing (DST) and diagnosis and initiation of treatment are crucial to prevent disease transmission and reduce related high morbidity and mortality.[2]

Studies from around the world have raised concerns over the high pre-diagnostic and pre-treatment attrition in MDR-TB diagnosis and treatment pathways (DTP).[3–9] Most of these studies were conducted in settings with the capacity for phenotypic diagnostic techniques, with a long turnaround time (TAT). A study from New Delhi, India, identified a significant decrease in TAT and pre-treatment loss to follow-up in 2014 after the introduction of line probe assay (LPA) technology, mainly attributed to a decrease in laboratory diagnostic time, although other operational issues were still of concern.[10] There have been limited efforts to systematically investigate the provider perspective and clinical or demographic factors associated with not undergoing testing.

This mixed-methods study was conducted in Puducherry, India, where there is a facility for molecular diagnostics, to assess the gaps and operational challenges in the DTP of presumptive MDR-TB patients identified between October 2012 and September 2013. The specific objectives of the study were 1) to determine the number of eligible presumptive MDR-TB patients, 2) to determine the number (proportion) among them examined for culture and DST and diagnosed as MDR-TB, 3) to determine the number (proportion) among those MDR-TB patients initiated on treatment, 4) to ascertain the delays in DTP and 5) to explore the programmatic, clinical and demographic factors associated with failure to complete the DTP.

METHODS

Study setting

General setting

The study was conducted in Puducherry District, Union Territory of Puducherry (population ~1 million), a coastal plain area in South India, where approximately 70% of the population is urban. The district has one tuberculosis unit and 21 designated microscopy centres (DMCs). Among the 21 DMCs, eight are located in medical colleges, one in a district hospital and 12 in primary/secondary health centres.

PMDT services

In Puducherry, PMDT services are provided in the Government Hospital for Chest Diseases, a district level tertiary public health care facility that includes diagnostic and treatment facilities. The diagnostic facility is the Intermediate Reference Laboratory (IRL) and is accredited by the RNTCP for phenotypic (solid/liquid culture and DST) and molecular (LPA) diagnostic techniques. Treatment is provided according to the RNTCP PMDT guidelines, which follow World Health

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TABLE 1 Data variables and source of data collection for presumptive/confirmed MDR-TB patients, October 2012–September 2013, Puducherry, India

Variable	Source	Operational definition
Date of eligibility for CDST, presumptive MDR-TB patient criteria, age in completed years, sex, TB registration number, year of registration, DMC name	Treatment register/ laboratory register	For sputum-positive patients, date of smear examination was the date of eligibility. For sputum-negative patients, date of treatment initiation was taken as date of eligibility. For those diagnosed with HIV first and TB later, date of eligibility depended on whether the patient was sputum-positive or -negative. For those with TB diagnosed first and then HIV, date of HIV testing was considered. For patients with known MDR-TB contacts, date of TB registration was considered
Whether referred for CDST, date of referral for CDST	Record maintained at DTC for referral or form for referral for CDST	If there was a record for referral maintained at DMC (copy of referral for CDST form) or DTC, then it was considered as 'referred'. In case of discrepancy in dates, earlier date was considered
Sputum received at IRL, date of sputum received at IRL, whether DST was performed, date of DST, DST result, date of DST result, date of dispatch of DST result to DTC	CDST register at IRL	Eligible presumptive MDR-TB patients tracked through their TB registration numbers, but for the IRL laboratory register, where TB registration number was not entered, patient's name and address was used. If IRL CDST register showed 'contaminated' as the result, and no further sample was received, it was registered as 'sample received but DST not done'
Whether patient was referred to DRTB centre from DTC; date of referral to DR-TB centre	Record maintained at DTC for referral	—
Whether treatment was initiated; date of treatment initiation	DOTS-Plus treatment register at DR-TB centre	—

MDR-TB = multidrug-resistant tuberculosis; CDST = culture and drug susceptibility testing; DMC = Designated Microscopy Centre; HIV = human immunodeficiency virus; TB = tuberculosis; DST = drug susceptibility testing; IRL = Intermediate Reference Laboratory; DTC = District Tuberculosis Centre; DR-TB = Drug-Resistant Tuberculosis Centre.

Organization (WHO) recommended strategies. In Puducherry, 'presumptive MDR-TB patients' include all retreatment TB patients, any follow-up smear-positive cases, new pulmonary TB patients who are contacts of known MDR-TB patients, and all human immunodeficiency virus (HIV) TB co-infected cases at diagnosis.[11] According to the guidelines, presumptive MDR-TB patients are identified at DMCs and sputum samples are sent to the IRL along with a request for culture and DST (CDST). Records on presumptive MDR-TB patients are maintained at the DMCs and at the district level.

Study design and population

This mixed-methods study had quantitative and qualitative components. The quantitative component consisted of a retrospective cohort analysis through record review of all presumptive MDR-TB patients residing in Puducherry identified between 1 October 2012 and 30 September 2013. The qualitative component included in-depth interviews of key informants involved in PMDT services.

Data variables, sources of data and data collection

Data collection was conducted during March–April 2014.

Quantitative data

A list of eligible presumptive MDR-TB patients was prepared based on the information from the DMC TB laboratory register and the TB treatment register at the District TB Centre (DTC). Each referral was tracked using a TB registration number in the records at the DTC, the CDST register (IRL) and the treatment register (DR-TB centre). The TB registration number was not recorded in the CDST register at the diagnostic facility and the name and address of the patient were used for tracking.

Data for each eligible presumptive MDR-TB patient (from identification to referral to testing and diagnosis) were reviewed for 3 months after the date of eligibility for DST. In cases where the LPA was invalid or the patient was sputum-negative, the period of record review was extended for 3 months from the date of receipt of the sputum sample at the IRL. Data variables, corresponding sources of data and the operational definitions used are summarised in Table 1.

Qualitative data

Programmatic factors were explored through key informant interviews with relevant stakeholders (purposive sampling): the State TB Officer (state programme manager), the Medical Officer-TB Control (sub-district programme manager for a population of 0.5 million), the Senior Treatment Supervisor (the paramedic responsible for recording and reporting TB treatment for a population of 0.5 million), the Senior TB Laboratory Supervisor (the paramedic responsible for maintaining the high quality of TB diagnosis at a microscopy centre for a population of 0.5 million), the DOTS-Plus treatment supervisor (the paramedic who coordinates with DR-TB patients and treatment centres for the initiation and follow-up of DR-TB treatment), the Auxiliary Nurse Midwife (the paramedic who facilitates implementation of national health programmes for a popu-

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The current analysis was conducted using part of data from the TB patient database maintained by the Revised National Tuberculosis Control Programme, Puducherry, India, and consists of patient data routinely collected in the programme. The database contains confidential information which we do not have permission to share. However, interested readers and researchers may request the data from the State TB Officer (stopd@rntcp.org), State TB cell, Directorate of Health services, Government of Puducherry.

Conflicts of interest: none declared.

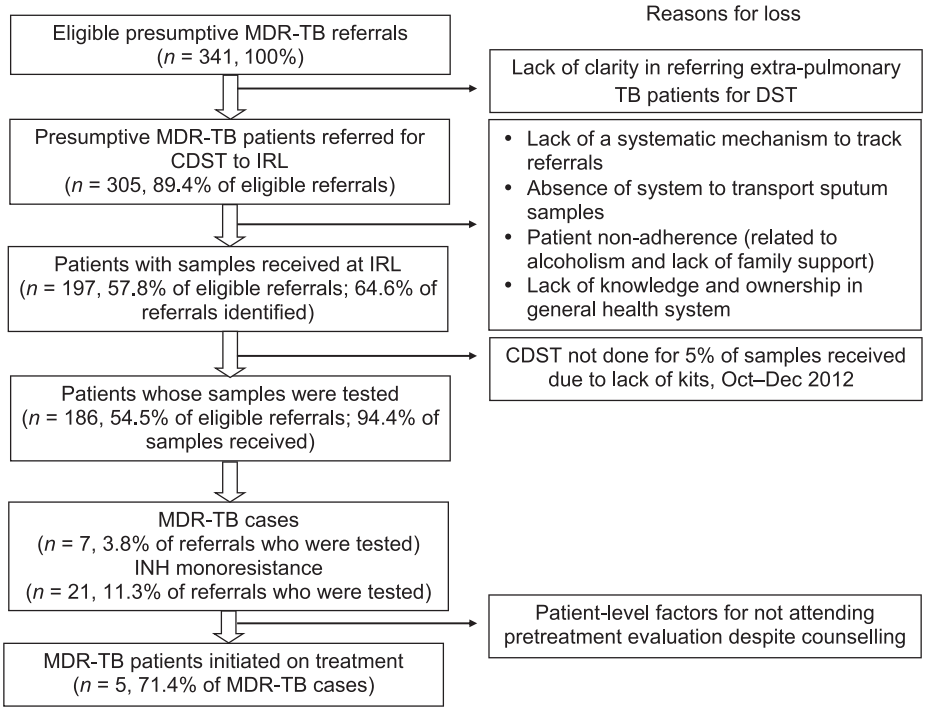

FIGURE Flow of presumptive MDR-TB patients in the diagnosis and treatment pathway (between October 2012 and September 2013), Puducherry, India. MDR-TB = multidrug-resistant tuberculosis; DST = drug susceptibility testing; CDST = culture and drug susceptibility testing; IRL = Intermediate Reference Laboratory; INH = isoniazid.

lation of 5000) and the diagnostic facility microbiologists (one each, for a total of seven). The principal investigator (HDS) was a faculty member (MBBS, MD in Community Medicine) in a medical college in the region and was trained in qualitative research.

The research goals were explained to the stakeholders. The principal investigator held one-to-one interviews at the participants' workplaces after obtaining their permission and consent to participate in the study. Only the participant and the researcher were present during the interview. An interview guide was pilot-tested and used to conduct the interviews. Prompts were provided for the participants if they had difficulties understanding or responding. As the participants did not consent to audio or video recording, the interviewer took verbatim notes during the interview and transcripts were prepared. The summary of the interviews was then read to the participants to ensure validation. The duration of the interviews ranged from 10 min to 1 hour. One repeat interview was carried out with the DOTS-Plus treatment supervisor. There were no drop outs.

Data management and statistical analysis

Quantitative data collected in a structured proforma were double-entered, validated and analysed using EpiData version 3.1 for entry and version 2.2.2.182 for analysis (EpiData Association, Odense, Denmark). Key analytic outputs were the number and proportion of presumptive MDR-TB patients at each step of DTP (Figure); the TAT in days for each step; and the association between not getting tested and various clinical and demographic factors. Mean and standard deviation, median and range, interquartile range, proportion, relative risks (adjusted for confounding wherever applicable using the Mantel-Haenszel method) and 95% confidence intervals (CI) were used to summarise the analytic output.

Thematic analysis was used to analyse the interview data. This approach in health-care research is flexible and appropriate for determining solutions to real-world problems.[12] The data obtained were compiled and the principal investigator read the transcripts to become familiar with the data. As the questions were open-ended, it allowed analysis to be inductive, with the codes emerging directly from the data. Similar codes were categorised and combined into themes. To ensure that the results were a reflection of the data, the themes were related back to the original data.[13] A second investigator reviewed the analysis to reduce bias and enhance interpretive credibility. As the data set was not large, we performed the analysis manually and did not use any software.

Ethics approval

Ethics approval was obtained from the Institutional Ethics Committee of the Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India, and the Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease, Paris, France. For the quantitative component of the study, which involved the retrospective review of patient records, a waiver for informed consent was obtained from the ethics committees. Written informed consent was obtained for the stakeholder interviews. The consent form had two parts: information for the participant and the actual consent form, which was signed by the participant in the presence of a witness. The ethics committees approved this consent procedure.

RESULTS

Quantitative data

During the study period, 341 eligible presumptive MDR-TB patients were identified by the investigators (Table 2). Of these, 291

TABLE 2 Clinical and demographic profile of presumptive MDR-TB patients, October 2012–September 2013, Puducherry, India

Variable	Presumptive MDR-TB patients *n* (%)
Age, years	
<14	2 (0.6)
14–44	183 (53.7)
45–64	132 (38.7)
⩾65	24 (7)
Sex	
Male	291 (85.3)
Female	50 (14.7)
Health facility	
PHC/CHC	59 (17.3)
District level	189 (55.4)
Medical college	76 (22.3)
Others*	17 (5)
Presumptive MDR-TB patients	
Retreatment	197 (57.8)
Relapse	98 (28.7
Default	44 (12.9)
Failure	21 (6.2)
Others	34 (10)
Follow-up smear-positive	122 (35.8)
New patient with TB-HIV	22 (6.5)
New pulmonary TB with known MDR-TB contact	0 (0)
Total	341 (100)

*Missing, tests performed outside Puducherry.
MDR-TB = multidrug-resistant tuberculosis; PHC = primary health centre; CHC = community health centre; TB = tuberculosis; HIV = human immunodeficiency virus.

(85.3%) were males, 197 (57.8%) were retreatment cases and 189 (55.4%) were referred from the district level (the Government Chest Clinic and the Government Hospital for Chest Diseases).

Of the 341 eligible presumptive MDR-TB patients, the programme referred 305 (89.4%), of whom 197 (64.6%) were received at the IRL. An additional 21 (6.9%) patients were reached after a follow-up period of 3 months from the date of eligibility. However, these were not considered in the final analysis. CDST results were available for 186 (94.4%) referrals. Among these, 5 (2.7%) were identified as MDR-TB (rifampicin [RMP] and isoniazid [INH] resistant), 2 (1.1%) as RMP monoresistant and 21 (11.3%) as INH monoresistant. Of the five MDR-TB and two RMP-resistant patients, five were registered and initiated on the DOTS-Plus regimen. Pre-diagnostic and pre-treatment attrition were 45.5% (155/341) and 29% (2/7), respectively. Among patients who completed the DTP, the time taken (in days) from referral to testing to diagnosis to treatment initiation is summarised in Table 3.

The following factors were associated with not undergoing testing: patients with extra-pulmonary tuberculosis (EPTB) (RR = 2.3), patients with HIV-TB co-infection (RR = 1.7), patients identified during October–December 2012 (RR = 1.3) and patients identified from primary or secondary health centres (RR = 1.8). Univariate analysis showed an association between female sex and not being tested, although stratified analysis showed that this was due to confounding by EPTB (Table 4).

Qualitative data

The themes that emerged following the analysis of key informant interviews and the verbatim quotes are summarised in Table 5.

TABLE 3 Turnaround time for various steps in diagnostic and treatment pathway of presumptive/confirmed MDR-TB patients, October 2012–September 2013, Puducherry, India

Variable	Patients* *n*	Days Median [IQR]
Days to refer from DMC after date of eligibility†	300	2.5 [1–4]
Days to receive sputum at IRL after referral	192	6 [0–22]
Days to test at IRL after receipt of sputum	186	2 [1–3]
Days to dispatch result from IRL after testing	123	2 [2–3]
Days to initiate treatment at DR-TB after dispatch of result	3	Min 18 days Max 35 days
Days to test at IRL after date of eligibility	181	11 [5–34]
Days to initiate treatment at DR-TB after testing	5	38 [29–39]
Days to initiate treatment at DR-TB after date of eligibility†	5	79 [79–125]

*Includes patients who completed the process, were eligible for the next step and whose dates were recorded.
†Date of eligibility for culture and drug susceptibility testing.
MDR-TB = multidrug-resistant tuberculosis; IQR = interquartile range; DMC = Designated Microscopy Centre; IRL = Intermediate Reference Laboratory; DR-TB = Drug-Resistant Tuberculosis Centre.

The operational issues that arose from the perspective and experiences of the interviewees are summarised below.

Reasons for non-referral

At the district level, there was a lack of clarity among the providers regarding the referral of EPTB cases (32/341 eligible referrals). Other than retreatment cases, the staff in the general health care delivery systems were not aware of the criteria for referral for CDST, especially between October 2012 and March 2013.

Reasons for not reaching a diagnostic facility

Lack of a mechanism to transport the sputum samples from the DMC to a diagnostic facility, such as a courier service, was identified as a constraint. It was perceived by the providers that there was no need for a courier service, as Puducherry is geographically small and patients could visit the diagnostic laboratory. Providers mentioned that a referral register was not maintained in the district, which prevented effective tracking of patients.

Most of the referrals were made from the Government Chest Clinic where the DTC was located. Patients were referred first to the Government Chest Clinic and then to the IRL. The two possible reasons for this cited by the providers were the patients' faith in the Government Chest Clinic and the opportunity to avoid being stigmatised by not visiting their nearest DMC. The CDST forms of patients referred from the major tertiary public health facilities (the Government Chest Clinic and the Government Hospital of Chest Diseases) did not contain the TB registration numbers, and these were therefore not entered in the diagnostic facility laboratory register.

Among the follow-up sputum-positive patients, there were chances that a patient was eligible more than once for DST; however, patients were not willing to go to the IRL more than once.

Reason for not testing

There was a reported shortage of testing kits from October to December 2012, which was soon rectified.

Reason for not initiating or for delays in initiating treatment

It was perceived that social factors, such as alcoholism and lack of family support, might have played a role in treatment initiation.

TABLE 4 Comparison of clinical and sociodemographic factors between eligible presumptive MDR-TB patients, October 2012–September 2013, Puducherry, India

Variable	No DST *n* (%)	DST *n* (%)	RR (95%CI)
Age, years			
<14	1 (50)	1 (50)	–
14–44	84 (45.9)	99 (54.1)	1.08 (0.84–1.39)
45–64	56 (42.4)	76 (57.6)	Reference
⩾65	14 (58.3)	10 (41.7)	1.38 (0.93–2.04)
Sex			
Male	124 (42.6)	167 (57.4)	Reference
Female	31 (62)	19 (38)	1.46* (1.13–1.88)
Health facility			
PHC/CHC	36 (61)	23 (39)	1.80 (1.35–2.40)
District level	64 (33.9	125 (66.1)	Reference
Medical college	41 (53.9)	35 (46.1)	1.59 (1.19–2.12)
Others†	14 (82.4)	3 (17.6)	2.43 (1.81–3.27)
Presumptive MDR-TB patients			
Retreatment	84 (42.6)	113 (57.4)	Reference
Follow-up smear-positive	55 (45.1)	67 (54.9)	1.05 (0.82–1.36)
New patient with TB-HIV	16 (72.7)	6 (27.3)	1.71 (1.26–2.31)
New pulmonary TB with known MDR-TB contact	–	–	–
Extra-pulmonary TB			
Yes	30 (93.8)	2 (6.3)	2.31 (1.97–2.73)
No	125 (40.5)	184 (59.5)	Reference
Quarter			
Oct–Dec 2012	53 (55.2)	43 (44.8)	1.33 (0.99–1.80)
Jan–Mar 2013	39 (41.5)	55 (58.5)	Reference
Apr–June 2013	28 (43.8)	36 (56.3)	1.05 (0.73–1.52)
July–Sept 2013	35 (42.7)	47 (57.3)	1.03 (0.72–1.46)
Total	173 (50.6)	169 (9.4)	–

*Adjusted for extra-pulmonary tuberculosis (RR = 1.17, 95%CI 0.91–1.50).
†Includes missing data and DMCs outside Puducherry.
MDR-TB = multidrug-resistant tuberculosis; DST = drug susceptibility testing; RR = relative risk; CI = confidence interval; HIV = human immunodeficiency virus; PHC = primary health centre; CHC = community health centre; DMC = designated microscopy centre.

There was a felt need either to incentivise the process or to link patients to existing social welfare schemes or alcohol de-addiction services. The flow of patients and the reason for loss of patients at each step are summarised in the Figure.

DISCUSSION

The pre-diagnostic attrition rate was high, with nearly half of presumptive MDR-TB patients not tested for CDST. Even among the seven MDR-TB patients diagnosed, two were not initiated on treatment.

Attrition occurred at every step of the diagnostic pathway. First, about 10% of patients with presumptive MDR-TB were not identified or referred for testing, an aspect missed by most of the other studies on this issue, and similar to an existing study from Andhra Pradesh, India.[9] Attrition at this stage was mainly seen among previously treated patients with EPTB (categorised as 'retreatment others'). This was predominantly due to a lack of clarity among the programme staff with respect to whether EPTB patients need to be referred. Even the national PMDT guidelines are not clear as to which specimens should be collected and the methods for storage and processing before sending to the laboratory.[11] The main cause of attrition, however, was the gap between referral and reaching the laboratory. Only about half of the patients were tested in our study, compared to 10% in Tanzania,[9] 39% in China,[5] 40% in Malawi,[7] 50% in Cambodia,[4] 64% in Andhra Pradesh, India,[9] 74% in Delhi, India[10] and 79% in Sri Lanka.[8] All the above studies took place in settings that used phenotypic diagnostic techniques. Variations worldwide could be due to differences in the criteria for presumptive MDR-TB or in the settings and phase of PMDT implementation. Furthermore, the period of review considered for each patient was not clear in other studies. Using a molecular diagnostic technique with a quick TAT is expected to lead to high test coverage. This was demonstrated by a study in Delhi, India, where test coverage of 95% was achieved following the introduction of LPA and reduced the time in testing.[10] In our study setting, despite using LPA, a test coverage of only ~50% was achieved, indicating that the technology alone cannot compensate for programmatic deficiencies.

The main programmatic reason for non-testing was the lack of a systematic mechanism for the tracking of referrals. The key document (a CDST register at district level) to be used for tracking referrals was not maintained, and the key patient identifier (TB registration number) required for tracking was not recorded consistently in all of the documents. Furthermore, only absolute numbers of patients tested were reviewed periodically, with no

TABLE 5 Perceived challenges by health care providers associated with not being tested and initiating treatment for presumptive/confirmed MDR-TB patients in Puducherry, India

	Major themes	Verbatim quotes
Patient level	Patient non-adherence: alcoholism, stigma, lack of family support	'People are lazy. Everything is free. Hence, patients don't value the services provided.'
		'Generally, these patients are alcoholic and do not have family support. The same factors play a role in patient not going to IRL for testing and not complying with DOTS-Plus treatment.'
		'Patients have faith in district-level hospital. There is associated stigma, patients avoid the same by not going to nearest DMC.'
		'It is patient-level factors which result in not getting tested. We are doing more than what is needed.'
		'Retreatment cases because of their previous bad experience and follow-up sputum-positive because of multiple possible referrals do not cooperate for going to IRL.'
Programme level	Lack of systematic mechanism to track referral for CDST	'Referral for CDST register was not maintained at district tuberculosis centre.'
		'Instead of referrals being identified at DMC and directly referred from there to IRL, what happens is that STS makes a line list of patients who are eligible for testing at district level for a period of time, say last 2 months, and asks the respective DMC to track the patients and refer them to IRL. Some patients in the meantime change address.'
	Absence of courier service to transport sputum to IRL	'Puducherry being a small district, we are not using courier system.'
	Lack of knowledge and ownership among staff of general health system	'Bulk of the referral is done from district level. PHIs also refer the suspect cases first to district level.'
		'Large load of TB patient management is shared by Government Chest Clinic and Government Hospital for Chest Diseases.'
		'Staff at PHI not completely aware of the screening criteria.'
		'We are not required to send samples in case of extra-pulmonary TB.'
	TB registration number entry in IRL register	'As some referral doesn't happen from PHI/DMC, TB registration number is not entered in referral form and same is the situation in IRL register. This makes it difficult to track patients.'
	Shortage of diagnostic kits	

MDR-TB = multidrug-resistant tuberculosis; IRL = Intermediate Reference Laboratory; DMC = Designated Microscopy Centre; CDST = culture and drug susceptibility testing; STS = Senior Treatment Supervisor; PHI = peripheral health institution.

cohort analysis. The high absolute numbers (which included those from previous years and from neighbouring states) led to a false sense of assurance among the programme managers that the programme was doing well in identifying and testing presumptive MDR-TB patients.

The other main reason for non-testing was the lack of a mechanism for sputum collection and transport. While the programme staff felt that Puducherry was a small area geographically and sputum transport was not required, patients from the hard-to-reach primary health centres might have had problems in reaching the laboratory, and sputum transport was identified as a significant factor associated with non-testing in quantitative data analysis.

The other reason for attrition was a temporary stock-out of LPA test kits, particularly during October–December 2012, which explains the higher attrition rate during that period. Patients with HIV-TB co-infection were more likely not to have been tested, again due to a lack of clarity in referring them (9/22 were not referred), and extra-pulmonary involvement (8/22). Patient non-adherence (related to alcohol abuse and lack of family support), suboptimal knowledge about the criteria for 'presumptive MDR-TB' and other PMDT guidelines, and lack of ownership among the general health system staff working in the peripheral health institutions were the other key operational issues identified.

The other issue of concern was the delays involved in the DTP. Among the MDR-TB patients started on treatment, the median time to initiation of treatment was high, at 79 days (n = 5). In the Delhi, India, study[10] (a setting with LPA), the median time to initiate treatment was 37 days, and in South Africa,[14] a setting where Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) is available, it was 17 days. The delay in our study is unacceptable, and steps are urgently needed to ensure the early initiation of treatment and break the chain of transmission.

Ineffective and inappropriate treatment,[15,16] treatment failure[17] in previously treated patients and contact with confirmed MDR-TB patients[17] are strong risk factors for developing MDR-TB. India's RNTCP recognises that the implementation of a good quality DOTS programme is the first priority for MDR-TB control in the country.[11] Preventing the emergence of MDR-TB in the community is of even greater priority than its treatment.[11] However, it is also important to identify and treat MDR-TB early enough to prevent further spread of resistance in the community, which is a challenge. The factors identified in our research may aid in resolving the challenges in the DTP.

Policy implications

Pre-diagnostic attrition could be a key reason for the low MDR-TB case detection rate globally and in India. According to the 2013 WHO TB report, there were an estimated 64 000 MDR-TB cases among notified TB patients in India in 2012, and only 16 588 cases were diagnosed, giving a case detection rate of just 26%.[1] If we consider the total estimated incidence of MDR-TB in India (~99 000 cases per year), the case detection rate would drop further, to 17%. Pre-diagnostic attrition needs to be addressed urgently if we are to make progress in improving MDR-TB case detection and achieve universal access to MDR-TB care.[12,13] Keeping this in mind, along with our study findings, we would like to make the following recommendations:

1 Improved mechanisms for tracking referrals: this includes setting up and strengthening the use of a 'referral for CDST' register at the DTC, the consistent recording of the TB registration number in the 'referral for CDST' form and in the IRL laboratory register to enable tracking and making cohort analysis of eligible patients part of routine monitoring of PMDT services. In addition, we recommend that the programme test innova-

tive models for tracking, including the use of mobile phone reminders[14] and electronic patient registers.[15]
2 Health system strengthening: this would include training and re-sensitising the staff of the general health care delivery system, especially DMC laboratory technicians, and developing a mechanism for sputum transport from the DMC to the IRL.
3 The programme may consider certain incentives or linking patients' existing social schemes with PMDT services to address patient-level factors.

The findings of our study were shared with the programme managers. Some of the presumptive MDR-TB patients in our cohort review who were not tested for DST have been re-traced. Two patients in our cohort who were not initiated on treatment during the study period have since been started on treatment. Some of the suggestions, such as using a 'referral for CDST' register at the DTC level and the systematic tracking of presumptive MDR-TB patients, have been implemented in the programme. Non-governmental organisations have provided support to transport sputum from hard-to-reach DMCs. A similar cohort review of presumptive MDR-TB patients in the year following the study will be required to determine whether this has had an impact on programme performance.

Limitations

There were some limitations to our study. Few patients from our cohort were eligible for the DOTS-Plus regimen (n = 7). The association of MDR-TB treatment outcomes and the occurrence of new MDR-TB cases among contacts with a delay in DTP were beyond the scope of this study. Record review studies have inherent limitations. However, the records in the RNTCP are monitored and supervised, including periodic data validation. Patient-level factors were identified through a programme perspective, which, as expected, tended to put the blame on the patient. However, it is important to understand the patient's perspective, and this research needs to be carried out in the near future. Randomised intervention trials could be established in the future to test the efficacy and impact of interventions to improve follow-up of referrals, introduce improved, rapid laboratory testing for MDR-TB and speed up treatment initiation after testing.

Strengths

The study had several strengths. This is the first study not only to assess the magnitude of attrition in DTP but also to add a qualitative component that systematically explored the reasons for attrition. This is the second study from India to identify gaps in DTP in a setting using LPA. The methodology used was robust, with pre-defined operational definitions for variables and a clear follow-up period defined for record review that was the same for each eligible referral in the cohort. The data were quality assured and robust, with double data entry and validation. As we studied the entire population of presumptive MDR-TB patients in Puducherry, without sampling, the results are likely to be representative, and thus reflect the ground reality for the region and have implications for policy. STROBE[16] and COREQ[17] guidelines were followed for the reporting of quantitative and qualitative aspects in the study.

CONCLUSION

In this operational research study, we found high pre-diagnostic and pre-treatment attrition among presumptive MDR-TB patients and identified several reasons for this. Despite the introduction of molecular diagnostic techniques, operational issues in MDR-TB screening remain a concern, and require urgent attention.

References

1 World Health Organization. Global tuberculosis report. WHO/HTM/TB/2013.11. Geneva, Switzerland: WHO, 2013. http://apps.who.int/iris/bitstream/10665/91355/1/9789241564656_eng.pdf Accessed April 2015.
2 World Health Organization. The Stop TB strategy: building on and enhancing DOTS to meet the TB-related Millennium Development Goals. WHO/HTM/TB/2006.3. Geneva, Switzerland: WHO, 2006. http://www.stoptb.org/assets/documents/resources/publications/plan_strategy/The_Stop_TB_Strategy_Final.pdf Accessed March 2015.
3 Kilale A M, Ngowi B J, Mfi G S, et al. Are sputum samples of retreatment tuberculosis reaching the reference laboratories? A 9-year audit in Tanzania. Public Health Action 2013; 3: 156–159.
4 Khann S, Mao E T, Rajendra Y P, et al. Linkage of presumptive multidrug resistant tuberculosis (MDR-TB) patients to diagnostic and treatment services in Cambodia. PLOS ONE 2013; 8: e59903.
5 Qi W, Harries A D, Hinderaker S G. Performance of culture and drug susceptibility testing in pulmonary tuberculosis patients in northern China. Int J Tuberc Lung Dis 2011; 15: 137–139.
6 Yagui M, Perales M T, Asencios L, et al. Timely diagnosis of MDR-TB under program conditions: is rapid drug susceptibility testing sufficient? Int J Tuberc Lung Dis 2006; 10: 838–843.
7 Harries A D, Michongwe J, Nyirenda T E, et al. Using a bus service for transporting sputum specimens to the Central Reference Laboratory: effect on the routine TB culture service in Malawi. Int J Tuberc Lung Dis 2004; 8: 204–210.
8 Abeygunawardena S C, Sharath B N, Van den Bergh R, et al. Management of previously treated tuberculosis patients in Kalutara district, Sri Lanka: how are we faring? Public Health Action 2014; 4: 105–109.
9 Chadha S S, Sharath B N, Reddy K, et al. Operational challenges in diagnosing multi-drug resistant TB and initiating treatment in Andhra Pradesh, India. PLOS ONE 2011; 6: e26659.
10 Singla N, Satyanarayana S, Sachdeva K S, et al. Impact of introducing the line probe assay on time to treatment initiation of MDR-TB in Delhi, India. PLOS ONE 2014; 9: e102989.
11 Government of India Ministry of Health & Family Welfare. Guidelines on programmatic management of drug resistant TB (PMDT) in India. New Delhi, India: Central TB Division, Directorate General of Health Services, Ministry of Health & Family Welfare, 2012. http://tbcindia.nic.in/pdfs/Guidelines for PMDT in India - May 2012.pdf Accessed March 2015.
12 Guest G, MacQueen K M, Namey E E. Applied thematic analysis. Los Angeles, CA, USA: SAGE Publications, Inc., 2012: pp 320.
13 Lincoln Y S, Guba E G. Naturalistic inquiry. New York, NY, USA: SAGE Publications Inc., 1985: pp 416.
14 Naidoo P, Du Toit E, Dunbar R, et al. A comparison of multidrug-resistant tuberculosis treatment commencement times in MDRTB*Plus* line probe assay and Xpert® MTB/RIF-based algorithms in a routine operational setting in Cape Town. PLOS ONE 2014; 9: e103328.
15 Faustini A, Hall A J, Perucci C A. Risk factors for multidrug resistant tuberculosis in Europe: a systematic review. Thorax 2006; 61: 158–163.
16 Espinal M A, Laserson K, Camacho M, et al. Determinants of drug-resistant tuberculosis: analysis of 11 countries. Int J Tuberc Lung Dis 2014; 5: 887–893.
17 Caminero J A. Multidrug-resistant tuberculosis: epidemiology, risk factors and case finding. Int J Tuberc Lung Dis 2010; 12: 869–877.
18 World Health Organization. Sixty-second World Health Assembly. Prevention and control of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis. WHA62.15. Geneva, Switzerland: WHO, 2009. apps.who.int/gb/ebwha/pdf_files/WHA62-REC1/WHA62_REC1-en.pdf Accessed March 2015.
19 Falzon D, Jaramillo E, Wares F, et al. Universal access to care for multidrug-resistant tuberculosis: an analysis of surveillance data. Lancet Infect Dis 2013; 13: 690–697.
20 Denkinger C M, Grenier J, Stratis A K, et al. Mobile health to improve tuberculosis care and control: a call worth making. Int J Tuberc Lung Dis 2013; 17: 719–727.
21 World Health Organization. Electronic recording and reporting for tuberculosis care and control. WHO/HTM/TB/2011.22. Geneva, Switzerland: WHO, 2012. http://whqlibdoc.who.int/publications/2012/9789241564465_eng.pdf Accessed March 2015.
22 Von Elm E, Altman D G, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Lancet 2007; 370: 1453–1457.
23 Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care 2007; 19: 349–357.

Contexte : Programme national révisé de Lutte contre la Tuberculose, Pondichéry, Inde, avec une structure de techniques de diagnostic moléculaire.
Objectif : Déterminer l'abandon préalable au diagnostic et préalable au traitement et leurs raisons parmi des patients présumés atteints de tuberculose multirésistante (TB-MDR).
Méthodes : Dans cette étude utilisant plusieurs méthodes, l'élément quantitatif consistait en une analyse de cohorte rétrospective, grâce à une revue de dossiers, de tous les patients présumés atteints de TB-MDR entre octobre 2012 et septembre 2013. L'élément qualitatif incluait des entretiens approfondis avec des informateurs clés impliqués dans la gestion programmatique des services de TB pharmacorésistante.
Résultats : Sur 341 patients présumés TB-MDR éligibles, le taux d'abandon avant le diagnostic et avant le traitement a été de 45,5% (155/341) et 29% (2/7), respectivement. Les patients atteints de TB extra-pulmonaire (RR = 2,3), de coïnfection par le virus de l'immunodéficience humaine et TB (RR = 1,7), inscrits entre octobre et décembre 2012 (RR = 1,3) et identifiés à partir de centres de santé primaires/secondaires (RR = 1,8) avaient moins de chances d'être testés. Les thèmes qui ont émergé lors de l'analyse des données qualitatives ont été « l'absence d'un mécanisme systématique de suivi des patients référés pour culture et test de pharmaco sensibilité », « l'absence de services de coursier pour transporter les crachats », « le manque de connaissances et d'appropriation du personnel de santé en général », « les ruptures de stock de kits de diagnostic » et « la non-adhérence du patient ».
Conclusion : En dépit de l'introduction de techniques de diagnostic moléculaire, les problèmes opérationnels de dépistage de la TB-MDR restent préoccupants et requièrent une attention urgente.

Marco de referencia: El Programa Nacional Revisado contra la Tuberculosis en Pondicherry, en la India, cuenta con capacidad técnica para realizar pruebas diagnósticas moleculares.
Objetivo: Determinar las tasas de abandono anterior al diagnóstico y antes de comenzar el tratamiento y analizar sus causas, en pacientes con presunción clínica de tuberculosis multidrogorresistente (TB-MDR).
Método: En el presente estudio se utilizaron métodos mixtos; el componente cuantitativo consistió en un análisis retrospectivo de cohortes, a partir de los expedientes de todos los pacientes atendidos con presunción diagnóstica de TB-MDR entre octubre del 2012 y septiembre del 2013. El componente cualitativo incluyó entrevistas exhaustivas a informantes clave que participaban en la gestión programática de los servicios de tuberculosis farmacorresistente.
Resultados: En los 341 pacientes con presunción diagnóstica de TB-MDR, que cumplían las condiciones del estudio, se observó una tasa de abandono anterior al diagnóstico del 45,5% (155/341) y un abandono anterior al comienzo del tratamiento del 29% (2/7). Fue menos probable que se practicaran las pruebas diagnósticas en los pacientes con TB extrapulmonar (RR = 2,3), coinfección por el virus de la inmunodeficiencia humana y TB (RR = 1,7), en los pacientes registrados de octubre a diciembre del 2012 (RR = 1,3) y los pacientes detectados en un centro de atención primaria o secundaria (RR = 1,8). Los aspectos que surgieron durante el análisis cualitativo fueron 'la falta de un mecanismo sistemático de seguimiento de los pacientes remitidos para cultivo y pruebas de sensibilidad a los medicamentos', 'la ausencia de un servicio de mensajería que transporte las muestras de esputo', 'la falta de conocimientos y de apropiación del trabajo en los miembros del personal del sistema de salud general', 'el desabastecimiento de los estuches diagnósticos' y 'el incumplimiento por parte de los pacientes'.
Conclusión: Pese a la introducción de las técnicas de diagnóstico molecular, persisten dificultades operativas en la detección de la TB-MDR que precisan atención urgente.

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